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(54) 【発明の名称】 潜在的な抗精神病薬としてのグリシン開裂システム阻害剤

(57) 【要約】

本発明は、グリシン開裂システムの阻害剤および、有効な抗精神病薬としてのこれらの使用に関する。本発明はさらに、精神病、疾病と関連する精神病、精神分裂病、アルツハイマー病または他の関連する精神病性障害を有するヒトを治療するための方法に関する。

【特許請求の範囲】

【請求項 1】 ヒト患者における精神病性障害の治療用医薬の製造のための、グリシン開裂システムの阻害剤の使用。

【請求項 2】 精神病性障害が、精神分裂病、大うつ病、躁うつ病障害、アルツハイマー病または心的外傷後ストレス症候群から選択される、請求項 1 に記載の使用。

【請求項 3】 阻害剤が、増大するNMDA受容体媒介神経伝達に影響する、請求項 2 に記載の使用。

【請求項 4】 グリシン開裂システムの阻害剤が、バルプロ酸塩およびシステアミンから選択される、請求項 1 ～ 3 に記載の使用。

【発明の詳細な説明】

【0001】

本発明は、グリシン開裂システムの阻害剤および、有効な抗精神病薬としてのこれらの使用に関する。本発明はさらに、精神病、疾病と関連する精神病、精神分裂病、アルツハイマー病または他の関連する精神病性障害を有するヒトを治療するための方法に関する。

【0002】

発明の背景および技術分野

グリシンは、中枢神経系における神経伝達物質である。ここで、ストリキニーネ感受性グリシン受容体が存在し、ここで、グリシンは、阻害神経伝達物質として作用する。さらに、NMDA受容体に位置するグリシン結合部位がある。ここで、グリシンは、興奮性コアゴニスト(coagonist)として作用する。グリシン受容体の完全な活性化のために、グルタミン酸塩およびグリシンの存在は、必須である。NMDAアンタゴニスト、例えばフェンシクリジン(PCP)および関連する薬剤(例えばケタミンまたはジソシルピン)は、ヒトボランティアにおいて、精神分裂病と区別し得ない症状を誘発する(Luby et al., 1959; Rosenbaum et al., 1959; BakkerおよびAmini, 1961)。即ち、これらは、精神分裂病の陽性、陰性および認知的観点を含む症状の範囲を誘発する(Krystal et al., 1994; Malhotra et al., 1996)。さらに、PCPは、精神分裂病を患っている患者において、症状の悪化を誘発する(Lathi et al., 1995; Malhotra et al., 1997)。PCP誘発感情的、認知的および挙動的变化は、精神分裂病の臨床的モデルを示す(Luby et al., 1962)のみならず、さらに、これらのモデル生物での精神分裂病の症状に似た症状を呈するマウスおよびラットにおけるPCP誘発挙動的变化は、現在では、しばしば、精神分裂病についての動物モデルを用い(例えばFreed et al., 1984)、種々の作用機構を有する多くの抗精神分裂病薬で確認された(例えばJackson et al., 1993; Gleason et al., 1997; Vanover, 1997; Krebs-Thomson et al., 1998)。マウスおよびラットを用いるこれらの動物モデルの中で、最も顕著なモデルは、精神分裂病および精神分裂病の認知欠損症状を明らかにする前パルス阻害のPCP誘発崩壊の陽性および陰性の症状を模するPCP誘発過

剰移動(hyperlocomotion)である。

【0003】

グリシン、グリシン（部分的）アゴニストと精神分裂病

グリシンおよびグリシン部位における部分的アゴニストは、臨床試験(D'Souza 1995)において評価されている。特に、高い用量のグリシンは、極めて有望な結果を与えた(Zylberman 1995およびHeresco-Levy 1999)。2つの二重盲検プラシーボ比較臨床試験において、経口的に与えられた0.4 g/kgおよび0.8 g/kgのグリシンおよびこれらの通常の抗精神病投薬により、陰性の症状がそれぞれ15%および30%改善されたことが示された。副作用において、変化は観察されなかった。

【0004】

D-シクロセリンの効果は、いくつかの臨床的試験において評価された。1つの臨床的試験において、15~250 mg/dのD-シクロセリンの用量が評価された。結果は、50 mg/dの用量が、精神分裂病患者において陰性の症状を減少させたことを示した(Goff 1995)。他の二重盲検プラシーボ比較臨床試験において、50 mg/dと共にこれらの有効用量の抗精神病薬は、陰性の症状において改善を示したことが見いだされた(Goff 1999)。

【0005】

グリシンおよびグリシン開裂システム

グリシンは、神経伝達物質であるのみならず、C-1 構築ブロックの主要な給源の1つである。これは、グリシン開裂システム(GCS)により異化作用されて、二酸化炭素、アンモニアおよびテトラヒドロ葉酸メチレンを生じる。

GCSは、4種の酵素から成る：

- グリシンデカルボキシラーゼ、Pタンパク質、
- 水素担体タンパク質、Hタンパク質、
- アミノメチルトランスフェラーゼ、Tタンパク質、
- ジヒドロリポアミドデヒドロゲナーゼ、Lタンパク質。

以下の反応図式が適用される(Kikuchi 1980)：

【化1】

さらに、本発明は、グリシン開裂システム阻害剤の投与が増大するNMDA受容体媒介神経伝達に影響する方法を提供する。

さらに、本発明の目的は、精神病性障害、例えば精神分裂病、大うつ病、躁うつ病障害、アルツハイマー病または心的外傷後ストレス症候群に向けられる医薬の製造のためのグリシン開裂システムの阻害剤の使用を提供することにある。

【0008】

本発明の説明

分布

ニワトリにおいて、GCS活性は、肝臓、腎臓および脳において見いだされたが、心臓または脾臓においては見いだされなかった。Pタンパク質mRNAは、肝臓、腎臓および脳において見いだされ、TおよびHタンパク質活性は、さらに腎臓および心臓において出現した。

ラット脳において、HおよびTタンパク質mRNAは、嗅球、大脳、海馬、小脳、脳幹および脊髄において見いだされた。Pタンパク質mRNAは、嗅球、大脳、海馬および小脳において豊富であった。このことは、NMDA受容体の分布に類似する(Kure 1997)。

【0009】

Pタンパク質

Pタンパク質は、ニワトリ肝臓から特徴づけされる(1500gの肝臓から、8mgのタンパク質が得られ、33,000Uに相当する)。この分子量は、208,000である。これは二量体であり、各々の単量体は、1分子のピリドキサルリン酸を担持している(Hiraya, 1980)。ニワトリおよびヒトPタンパク質の単量体は、クローン化された。構造的相同性は、84である。Asp→Glu、Arg→LysおよびSer→Thrの変化を考慮せずに、構造的相同性は、93%程度に高い(Kume 1991)。ニワトリと大腸菌酵素との間の相同性は、53%である(Kure 1997)。

【0010】

グリシン開裂システムの既知の阻害剤および動物モデルにおける活性

バルプロ酸塩(抗痙攣薬、EMD49461)は、GCSを阻害することが知

られている(Martin-Gallardo 1985)。Kiは、肝臓および脳ミトコンドリアにおいて、それぞれ0.59mM、2mMである。ラットにおける720mg/kgのl.p.投与の結果、血液、肝臓、脳および脊髄中のグリシンレベルが、対照ラットの約140%に上昇した。システアミン(EMD247714)は、既知のGCS阻害剤である(IC50 約60μM、Lowry 1986)。8日齢のラットにおける250mg/kgのシステアミンのl.p.投与により、皮質中のグリシンの、対照動物の360%への増大が生じた(Iwama 1997)。他の弱い阻害剤は、アミノアセトニトリルおよびプロバルギルアミンである(Benavides 1983)。

【0011】

PCP誘発過剰移動モデルについて、本発明者等は、X-Y軸を制御する2つの一連の等間隔の赤外線光線を備え、マイクロコンピュータに接続された透明なプレキシガラス箱(45cm×45cm)からなる試験装置を用いる。PCP投与に続いて、30分間隔で、合計90分にわたり、移動距離(経路)[m]、および移動または休止に費やされた時間[秒]を、自動的に測定した。グリシン開裂システム、バルプロ酸塩およびシステアミンの阻害のための既知のモデル物質を、PCP投与の前に非経口的に投与する(PCP5mg/kgを腹腔内に投与する)。示した用量のPCPは、対照動物と比較して、移動距離または時間により測定して、約200~250%の増大と共に過剰のロコモーター挙動を誘発する。バルプロ酸塩およびシステアミンを、100~500mg/kgの用量で用いた。バルプロ酸塩およびシステアミンは、共に、試験した種々の用量においてPCP誘発過剰移動を低減し(図参照)、抗精神分裂病作用を示す。

【0012】

限定されたデータのみが、前パルス阻害(PPI)のPCP誘発崩壊の一層最近に確立されたモデルのみについて入手可能である。本発明者等の知識では、グリシンアゴニストR-(+)-HA-966およびグリシン輸送アンタゴニストD-シクロセリンのみが、現在検査され、PCP誘発PPIの反転を例証している(KretschmerおよびKoch, 1997; Furuya et al., 1998)。

投与刺激剤として用いられるPCPまたは関連する薬剤を有する過剰移動モデルにおいて、グリシン自体、グリシンアゴニストR-(+)-3-アミノ-1-

ヒドロキシピロリド-2-オン (R-(+)-HA-966)、部分的アゴニストD-シクロセリンまたはグリシン輸送剤アンタゴニストグリシルドデシルアミン (GDA) の効率は、齧歯動物において繰り返し例証された (例えばTothおよびLajtha, 1986; Toth et al., 1986; Singh et al., 1990; Kretschmer et al., 1992; Carlsson et al., 1994; Javitt et al., 1997; Nilsson et al., 1997; Javitt et al., 1999)。

【0013】

PPIのPCP誘発崩壊について、本発明者等は、マイクロコンピュータに接続された驚異的応答測定装置を備えた音減衰試験箱からなる市場で入手できる標準的な装置(Coulbourn Instruments, USA)を用いる; 白色ノイズ発生装置は、実験の間一定のレベルの背景ノイズを適用する。習慣期間の後、一連の70の組み合わせの前パルス (前パルスなし、または背景ノイズより8~6 dB高い) およびパルス (90~126 dB) を、ラットに無秩序に適用する。グリシン開裂システム、バルプロ酸塩およびシステアミンの阻害のための既知のモデル物質を、PCP投与の前に経口的に投与する (PCP 1~5 mg/kgを皮下投与する)。対照動物において、前パルスの提示は、パルスのみにより誘発された驚異的応答を阻害する。示した用量のPCPは、対照動物と比較して、最大約70%だけPPIの崩壊を誘発する。前に示した用量を、バルプロ酸塩およびシステアミンについて用い、PCP投与の前に投与する。バルプロ酸塩およびシステアミンは、共に、PPIのPCP誘発崩壊を、試験した種々の用量における種々の前パルス/パルス組み合わせにおいて逆転させ、抗精神分裂病作用を示す。

【0014】

グリシンの神経伝達ドーパミンとの複合相互作用が、未だ完全に理解されていないが、中枢神経系において、少なくとも部分的にGABA作動性およびコリン作動性介在ニューロンを介してのグリシンおよびドーパミンの反対平衡効果 (対称的な両側変化) は、長期間にわたり十分に知られている (例えばCheramy et al., 1978; Giurgieff et al., 1979; Leviel et al., 1979; SchmidtおよびKretschmer, 1997; Nankai et al., 1998)。ドーパミンアンタゴニストは、最高級の抗精神分裂病薬であり、作用のドーパミン作動性機構を有する抗精神分裂病薬に

ついて試験するための従来の動物モデルは、型通りの挙動、例えばドーパミンアゴニスト薬剤、例えばアボモルフィンの適用による、マウスにおける上昇挙動の誘発を用いる(Protais et al., 1976; Puech et al., 1978)。

【0015】

マウスにおける上昇試験を用いて、本発明者等は、以前に、グリシン輸送体阻害剤GDAおよび部分的グリシンアゴニストD-シクロセリンが、マウスにおけるアボモルフィン(1.25mg/kg、皮下に投与された)誘発上昇挙動を阻害したことを見いだした。従って、前に示した用量のモデル化合物であるシステアミンを、マウスにおける上昇試験においても検査する。再び、驚異的なことに、システアミンは、アボモルフィン攻撃の前に与えられた際に、500mg/kgのED50値(アボモルフィン誘発上昇を50%阻害する用量)を有する種々の用量において、アボモルフィン誘発上昇を阻害し、さらに抗精神分裂病作用を示す。

【0016】

これらの知見から、グリシン開裂システムの阻害剤を、精神病性障害、例えば精神分裂病、分裂病質または分裂病性人格障害、精神病に関連する障害、例えば大うつ病または躁うつ病、アルツハイマー病および心的外傷後ストレス症候群の治療のために直接用いることが示唆される。阻害剤は、単独で、または通常の抗精神病薬と共に投与することができる。

【0017】

【外1】

文献

- Bakker and Amini, Compr. Psychiatry 2, 1961, 269.
- Benavides J., et al., Biochem. Pharmacol. 32, 1983, 287.
- Carlsson et al., J Neural Transm - Gen Sect 95, 1994, 223.
- Cheramy et al., Eur J Pharmacol 47, 1978, 141.
- D'Souza D.C. et al., CNS Drugs Rev. 1, 1995, 227.
- Freed et al., Neuropharmacology 23, 1984, 175.
- Furuya et al., Brain Res 781, 1998, 227.
- Giorgueff et al., J Physiol 75, 1979, 611.
- Gleason et al., Psychopharmacology 129, 1997, 79.
- Goff D.C. et al., Arch. Gen. Psychiatry 56, 1999, 21.
- Goff, D.C. et al., Am. J. Psychiatry. 152, 1995, 1213.
- Heresco-Levy U., Arch. Gen. Psychiatry 56, 1999, 29.
- Hiraya et al., J. Biolog. Chem. 255, 1980, 11664.
- Iwama H., et al., Biochem. Biophys. Res. Commun. 231, 1997, 793.
- Jackson et al., Pharmacol Biochem Behav 48, 465.
- Javitt et al., Biol Psychiatry 45, 1999, 668.
- Javitt et al., Neuropsychopharmacology 1997, 17, 202.
- Kikuchi Goro, et al. Biochem. Soc. Transactions, 1980, 504.

【0018】

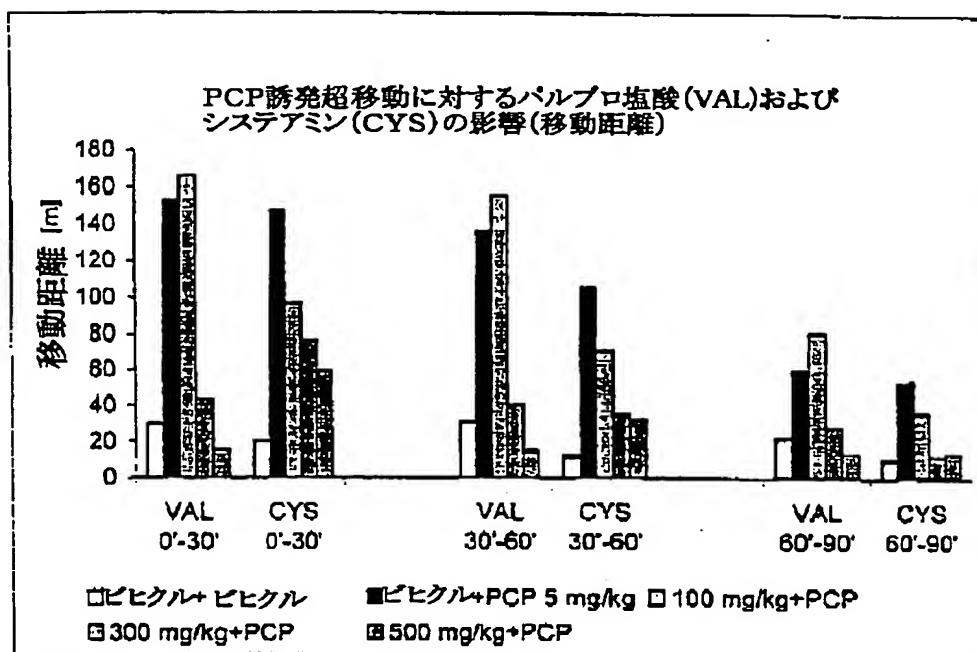
【外2】

Krebs-Thomson et al., Neuropsychopharmacology 18, 1998, 339
 Kretschmer and Koch, Psychopharmacology 130, 1997, 131.
 Kretschmer et al., J Neural Transm 87, 1992, 23.
 Krystal et al., Arch Gen Psychiatry 51, 1994, 199.
 Kume A., et al., J. Biol. Chem. 266, 1991, 3323.
 Kure S., et al., Jpn. J. Human Genet., 42, 1997, 13.
 Lathi et al., Neuropsychopharmacology 13, 1995, 9.
 Leviel et al., Brain Res 175, 1979, 259.
 Luby et al., Am J Psychiatry 119, 1962, 61.
 Luby et al., Arch Neurol Psychiatry 81, 1959, 363.
 Malhotra et al., Neuropsychopharmacology 14, 1996, 301.
 Malhotra et al., Neuropsychopharmacology 17, 1997, 141.
 Martin-Gallardo, et al., Biochem. Pharmacol. 34, 1985, 2877.
 Nankai et al., Prog Neuropsychopharmacol Biol Psychiatry 22, 1998, 35.
 Nilsson et al., J Neural Transm 104, 1997, 1195.
 Pratais et al., Psychopharmacology 50, 1976, 1.
 Puech et al., Eur J Pharmacol 50, 1978, 291.
 Rosenbaum et al., Arch Gen Psychiatry 1, 1959, 651.
 Schmidt and Kretschmer, Neurosci Biobehav Rev 21, 1997, 381.
 Singh et al., Proc Natl Acad Sci USA 87, 1990, 347.
 Toth and Lajtha, Neurochem Res 11, 1986, 393.
 Toth et al., Res Commun Psychol Psychiatry Behav 11, 1986, 1.
 Vanover, Eur J Pharmacol 332, 1997, 115.
 Zylberman I. et al., N.Y. Acad. Sci. 757, 1995, 487.

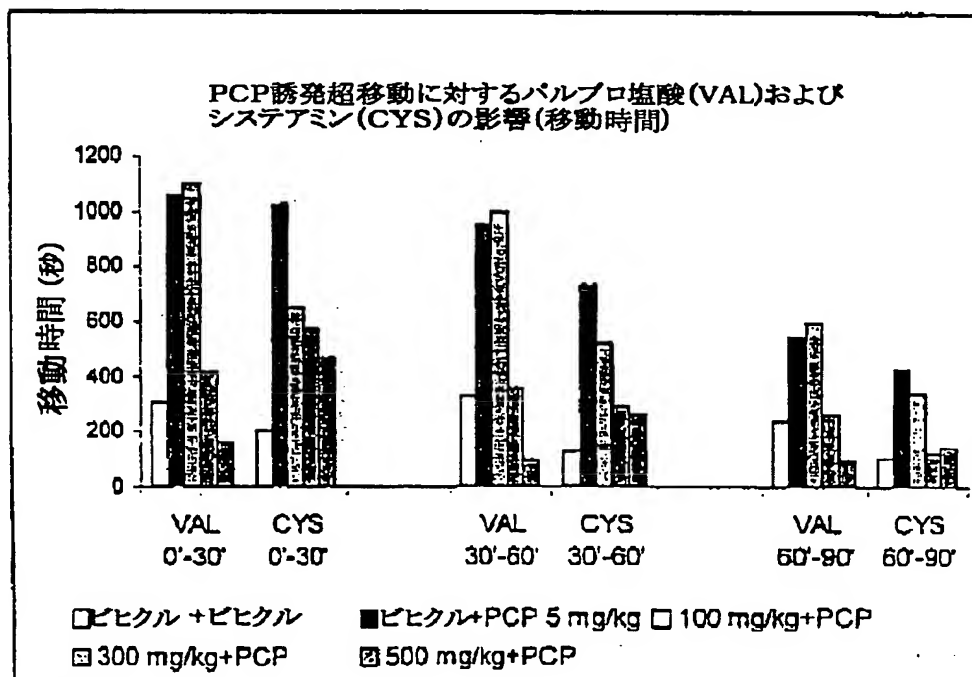
【図面の簡単な説明】

【図1】 PCP誘発過剰移動に対するバルプロ酸塩（VAL）およびシステアミン（CYS）の影響を示す。上側パネル：移動距離、下側パネル：移動時間。詳細は前記の通りである。

【図1】



(A)



(B)

INTERNATIONAL SEARCH REPORT

Inter. Appl. No. PCT/EP 00/03456		
A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/19 A61K31/13 A61P25/18 A61P25/24 A61P25/28		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) BIOSIS, EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHNEIDER L.S. ET AL: "Mechanism of action and prospects for cognitive enhancing medications" MEDICAL CLINICS OF NORTH AMERICA, vol. 78, no. 4, 1994, pages 911-934, XP000917566 page 916; table 2	1-4
X	MARK R. J. ET AL: "Anticonvulsants attenuate amyloid beta-peptide neurotoxicity, Ca2+ deregulation, and cytoskeletal pathology" NEUROBIOLOGY OF AGING, vol. 16, 1995, pages 187-198, XP000917338 abstract	1-4
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Date of the actual completion of the international search 7 September 2000		Date of mailing of the international search report 21/09/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3018		Authorized officer Seegert, K

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INTERNATIONAL SEARCH REPORT

 Intern. Appl. No.
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C.(CONTINUATION) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; Database accession no. prev199699205075 XP002146798 abstract & TAKAHASHI M. ET AL: "Case report of sodium valproate treatment of aggression associated with Alzheimer's disease" BRAIN AND NERVE (TOKYO), vol. 48, 1996, pages 757-760,	1-4
X	KECK P.E. ET AL: "Anticonvulsants and antipsychotics in the treatment of bipolar disorder" JOURNAL OF CLINICAL PSYCHIATRY, vol. 59, 1998, pages 74-81, XP000917401 "Valproate" page 74 -page 75	1-4
X	DAVIS L.L. ET AL: "Valproate as an antidepressant in major depressive disorder" PSYCHOPHARMACOLOGY BULLETIN, vol. 32, 1996, pages 647-652, XP000917554 abstract	1-4
X	HOLTZER C.D. ET AL: "Valproate in the treatment of acute mania" JOURNAL OF PHARMACY TECHNOLOGY, vol. 12, 1996, pages 6-11, XP000917438 page 11, last paragraph	1-4
X	HAYES S.G. ET AL: "Long-term use of valproate in primary psychiatric disorders" JOURNAL OF CLINICAL PSYCHIATRY, vol. 50, 1989, pages 35-39, XP000917324 abstract	1-4
X	MORINIGO A. ET AL: "Treatment of resistant schizophrenia with valproate and neuroleptic drugs" HILLSIDE JOURNAL OF CLINICAL PSYCHIATRY, vol. 11, 1989, pages 199-208, XP000917396 abstract	1-4
X	WO 94 05280 A (SALIM AWS SHAKIR MUSTAFA) 17 March 1994 (1994-03-17) claims	1-4
P, X	WO 99 49860 A (ENDOWMENT RES INHUMAN BIOLOGY ; VALLEE BERT L (US); MARET WOLFGANG) 7 October 1999 (1999-10-07) claims 22-34	1-4

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page 2 of 2

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Information on patent family members

International Application No.

PCT/EP 00/03456

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9405280	A	17-03-1994	AU	4975193 A	29-03-1994
WO 9949860	A	07-10-1999	AU	3470399 A	18-10-1999

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(81) 指定国 EP(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, I T, LU, MC, NL, PT, SE), OA(BF, B J, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG), AP(GH, GM, K E, LS, MW, SD, SL, SZ, TZ, UG, ZW), EA(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, C R, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, K Z, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, S K, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW			
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Fターム(参考)	4C084 AA17 NA14 ZA021 ZA121 ZA151 ZA161 ZA181 ZC201 4C206 AA01 AA02 DA03 JA22 MA01 MA04 NA14 ZA02 ZA12 ZA15 ZA16 ZA18 ZC20		

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/19, 31/13, A61P 25/18, 25/24, 25/28		A1	(11) International Publication Number: WO 00/66110 (43) International Publication Date: 9 November 2000 (09.11.00)
(21) International Application Number: PCT/EP00/03456 (22) International Filing Date: 17 April 2000 (17.04.00) (30) Priority Data: 60/131,647 29 April 1999 (29.04.99) US 99108480.7 30 April 1999 (30.04.99) EP (71) Applicant (for all designated States except US): MERCK PATENT GMBH [DE/DE]; Frankfurter Strasse 250, D-64293 Darmstadt (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): ARLT, Michael [DE/DE]; Friedrich-Ebert-Strasse 73, D-64342 Seeheim (DE). BAR-TOSZYK, Gerd [DE/DE]; Kreuzstrasse 57, D-64331 Weierstadt (DE). (74) Common Representative: MERCK PATENT GMBH; D-64271 Darmstadt (DE).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: GLYCINE CLEAVAGE SYSTEM INHIBITORS AS POTENTIAL ANTIPSYCHOTICS			
(57) Abstract The invention relates to inhibitors of the glycine cleavage system and their use as potential antipsychotic agents. The invention relates furthermore to a process for treating humans having psychosis, psychosis associated with an illness, schizophrenia, Alzheimer's disease or other related psychotic disorders.			

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Glycine Cleavage System Inhibitors as Potential Antipsychotics

The invention relates to inhibitors of the glycine cleavage system and their use as
5 potential antipsychotic agents. The invention relates furthermore to a process for
treating humans having psychosis, psychosis associated with an illness,
schizophrenia, Alzheimers disease or other related psychotic disorders.

BACKGROUND AND TECHNICAL FIELD OF THE INVENTION

10 Glycine is a neurotransmitter in the central nervous system. There, strychnine
sensitive glycine receptors exist, where glycine serves as an inhibitory
neurotransmitter. In addition there is a glycine binding site located at the NMDA
receptor. Here, glycine serves as a excitatory coagonist. For the full activation of
the glycine receptor the presence of glutamate and glycine is mandatory.

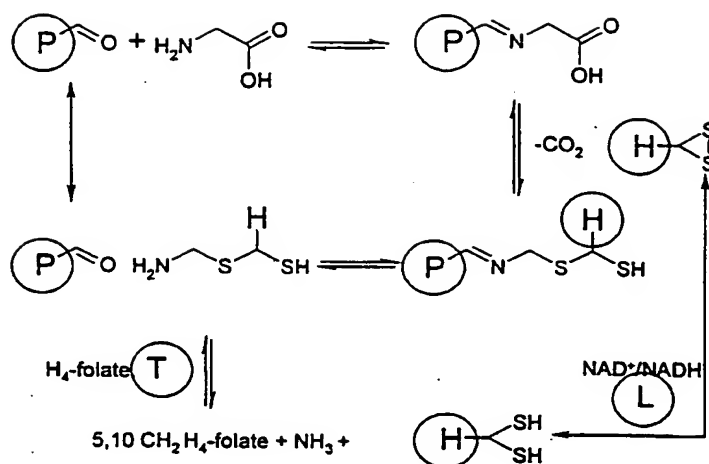
15 NMDA Antagonists such as phencyclidine (PCP) and related drugs (e.g.
ketamine or dizocilpine) induce symptoms in human volunteers which are not
distinguishable from schizophrenia (Luby et al., 1959; Rosenbaum et al., 1959;
Bakker and Amini, 1961), i.e. they induce a spectrum of symptoms including the
positive, negative and cognitive aspects of schizophrenia (Krystal et al., 1994;
20 Mulhotra et al., 1996). In addition, PCP provokes an exacerbation of symptoms in
patients suffering from schizophrenia (Lathi et al., 1995; Malhotra et al., 1997).
PCP-induced emotional, cognitive and behavioural changes represent not only a
clinical model of schizophrenia (Luby et al., 1962), but moreover PCP-induced
behavioural changes in mice and rats mimicking the symptoms of schizophrenia
25 in these model organisms are now frequently used animal models for
schizophrenia (e.g. Freed et al., 1984) and have been validated with many
antischizophrenic drugs with different mechanisms of action (e.g. Jackson et al.,
1993; Gleason et al., 1997; Vanover, 1997; Krebs-Thomson et al., 1998).
Amongst these animal models utilizing mice and rats, the most prominent models
30 are PCP-induced hyperlocomotion to model the positive and negative symptoms
of schizophrenia and PCP-induced disruption of prepulse inhibition revealing the
cognition deficit symptoms of schizophrenia.

Glycine, Glycine (Partial) Agonists and Schizophrenia

- Glycine and partial agonists at the glycine site have been evaluated in clinical trials (D'Souza 1995). In particular high doses of glycine gave very promising results (Zylberman 1995 and Heresco-Levy 1999). In two double blind, placebo controlled clinical studies it was shown that 0.4g/kg and 0.8g/kg glycine given orally along with their usual antipsychotic medication ameliorated negative symptoms by 15% and 30%, respectively. No changes were observed in side effects.
- 10 The effects of D-cycloserine were evaluated in several clinical trial. In one clinical trial doses from 15 to 250mg/d of D-cycloserine were assessed. The results showed that the dose of 50 mg/d reduced negative symptoms in schizophrenic patients (Goff 1995). In another double blind, placebo-controlled clinical trial it was found that 50mg/d along with their effective dose of antipsychotics gave an improvement in negative symptoms (Goff 1999).

Glycine and the Glycine Cleavage System

- Glycine is not only a neurotransmitter but also one of the major sources of C-1 building blocks. It is catabolized by the Glycine Cleavage System (GCS) to yield carbon dioxide, ammonia and methylene tetrahydrofolate.
- 20 The GCS consists of four enzymes:
- glycine decarboxylase, P-protein,
 - hydrogen carrier protein, H-protein
 - aminomethyltransferase, T-protein,
 - 25 -dihydrolipoamide dehydrogenase, L-protein,
- The following reaction scheme applies (Kikuchi 1980):



In vitro it is possible to substitute the H-protein with lipoic acid (Hiraya 1980).

5 SUMMARY OF THE INVENTION

The invention relates to inhibitors of the glycine cleavage system and their use as potential antipsychotic agents. It could be shown that, for example, valporate and cysteamine are potential inhibitors. The invention relates furthermore to a process for treating humans having psychosis, psychosis associated with an illness, schizophrenia, Alzheimers disease or other related psychotic disorders.

Therefore, it is an object of the invention to provide a process for treating a psychotic disorder in a human patient which comprises administering to said human a sufficient amount of an inhibitor, preferably valporate and / or cysteamine, of the glycine cleavage system.

In detail, the invention provides a process, wherein the psychotic disorder is schizophrenia, major depression, manic-depressive disorder, Alzheimers disease or post-traumatic stress syndrome.

Furthermore, the invention provides a process, wherein administering the glycine cleavage system inhibitor affects augmenting NMDA receptor-mediated neurotransmission.

Furthermore, it is an object of this invention to provide the use of inhibitors of the glycine cleavage system for the manufacture of a medicament directed to psychotic disorders like schizophrenia, major depression, manic-depressive disorder, Alzheimers disease or post-traumatic stress syndrome.

5

DESCRIPTION OF THE INVENTION

Distribution

In chicken GCS activity was found in liver, kidney and brain but not in heart or spleen. P-protein mRNA was found in liver, kidney and brain, T- and H-protein activity appeared additionally in kidney and heart.

10

In the rat brain H- and T-protein mRNA were found in olfactory bulb, cerebrum, hippocampus, cerebellum, brainstem and spinal cord. P-protein mRNA was abundant in olfactory bulb, cerebrum, hippocampus and cerebellum. This parallels the distribution of NMDA receptors (Kure 1997).

15

P-Protein

The P-protein was characterized from chicken liver (1500g of liver yielded 8 mg of protein corresp. to 33.000 U). Its molecular weight is 208.000. It is a homodimer, each monomer carrying one molecule of pyridoxalphosphate (Hiraya, 1980). The monomers of the chicken and human P-protein have been cloned. Structural homology is 84. Disregarding changes Asp->Glu, Arg->Lys and Ser->Thr strucural homology is as high as 93% (Kume 1991). The homology between the chicken and the E. Coli enzyme is 53% (Kure 1997).

20

25 Known Inhibitors of the Glycine Cleavage System and Activity in Animal Models

Valproate (anticonvulsive drug, EMD 49461) is known to inhibit the GCS (Martin-Gallardo 1985). The Ki is 0.59mM, 2mM in liver and brain mitochondria, respectively. I.p. administration of 720 mg/kg in rats resulted in an elevation of glycine levels in blood, liver, brain and spinal cord to appr. 140% of control rats. Cysteamine (EMD 247 714) is an known GCS inhibitor (IC50 appr. 60?M, Lowry 1986). I.p. administration of 250 mg/kg Cysteamine in 8 day old rats caused an increase of glycine in the cortex to 360% of the control animals (Iwama 1997).

30

Other weak inhibitors are aminoacetonitrile and propargylamine (Benavides 1983).

For the PCP-induced hyperlocomotion model we use a test apparatus consisting of a clear plexiglas box (45 cm x 45 cm) equipped with two series of equally spaced infrared beam lights controlling X-Y axes and connected to a microcomputer. Measured automatically are the distance (way) traveled [m], and the time spent with locomotion or resting [sec] in intervals of 30 min over a total of 90 minutes following PCP administration. The known model substances for inhibition of the glycine cleavage system, valproate and cysteamine, are administered parenterally before the PCP challenge (PCP 5 mg/kg administered intraperitoneally). PCP at the indicated dose induces excessive locomotor behavior with an increase of about 200 - 250% measured by either locomotion distance or time compared to control animals. Valproate and cysteamine were used at doses from 100 to 500 mg/kg. Both valproate and cysteamine reduce PCP-induced hyperlocomotion at various doses tested (see figures) indicating an antischizophrenic action.

Only limited data is available for the only more recently established model of PCP-induced disruption of prepulse inhibition (PPI). To our knowledge, only the glycine agonist R-(+)-HA-966 and the glycine transporter antagonists D-cycloserine have so far investigated and demonstrated a reversal of PCP-induced PPI (Kretschmer and Koch, 1997; Furuya et al., 1998).

In the hyperlocomotion model with PCP or related drugs used as challenge stimulants, the efficacy of glycine itself, the glycine agonist R-(+)-3-amino-1-hydroxypyrrolid-2-one (R-(+)-HA-966), the partial agonist D-cycloserine or the glycine transporter antagonist glycyldodecylamide (GDA) have been repeatedly demonstrated in rodents (e.g. Toth and Lajtha, 1986; Toth et al., 1986; Singh et al., 1990; Kretschmer et al., 1992; Carlsson et al., 1994; Javitt et al., 1997; Nilsson et al., 1997; Javitt et al., 1999).

For the PCP-induced disruption of PPI we use a commercially available standard equipment (Coulbourn Instruments, USA) consisting of a sound attenuated test box equipped with a startle response measuring unit connected to a

microcomputer; a white noise generator applies a constant level of back ground noise during the experiment. After a habituation period, a series of 70 combinations of prepulses (no prepulse or 8 to 6 dB above back ground noise) and pulses (90 to 126 dB) is randomly applied to the rats. The known model substances for inhibition of the glycine cleavage system, valproate and cysteamine, are administered parenterally before the PCP challenge (PCP 1 - 5 mg/kg administered subcutaneously). In control animals, presentation of the prepulse inhibits the startle response elicited by the pulse alone. PCP at the indicated doses induces a disruption of PPI by a maximum of about 70% compared to control animals. The doses indicated above are used for valproate and cysteamine, administered before the PCP challenge. Both valproate and cysteamine reverse PCP-induced disruption of PPI at different prepulse/pulse combinations at various doses tested indicating an antischizophrenic action.

Although the complex interaction of glycine with the neurotransmitter dopamine is not yet fully understood, the counterbalancing effects (symmetric bilateral changes) of glycine and dopamine, at least in part via GABAergic and cholinergic interneurons, in the central nervous system are well known for long (e.g. Cheramy et al., 1978; Giorguieff et al., 1979; Leviel et al., 1979; Schmidt and Kretschmer, 1997; Nankai et al., 1998). Dopamine antagonists are the classic antischizophrenic drugs, and conventional animal models to test for antischizophrenic drugs with a dopaminergic mechanism of action use the induction of stereotyped behaviours such as climbing behavior in mice by the application of dopamine-agonistic drugs such as apomorphine (Protais et al., 1976; Puech et al., 1978).

Using the climbing test in mice, we previously found that the glycine transporter inhibitor GDA and the partial glycine agonist D-cycloserine inhibited apomorphine (1.25 mg/kg administered subcutaneously)-induced climbing behavior in mice. Therefore the model compound cysteamine at the doses indicated before are investigated in the climbing test in mice, too. Surprisingly again, cysteamine when given prior to the apomorphine challenge inhibit apomorphine-induced climbing at various doses with an ED50 value (dose which inhibits apomorphine-

induced climbing by 50%) of 500 mg/ kg further indicating an antischizophrenic action.

From these findings it is suggested to use inhibitors of the glycine cleavage system directly for the treatment of psychotic disorders like schizophrenia, schizoid or schizotypal personality disorders, disorders associated with psychosis such as major or manic depression, Alzheimers disease and post-traumatic stress syndroms. The inhibitors can be administered alone or together with usual antipsychotic drugs.

10

Fig. 1 depicts the effect of valporate (VAL) and cysteamine (CYS) on PCP induced hyperlocomotion, Upper panel: traveled distance, lower panel: locomotion time. Detailed description above.

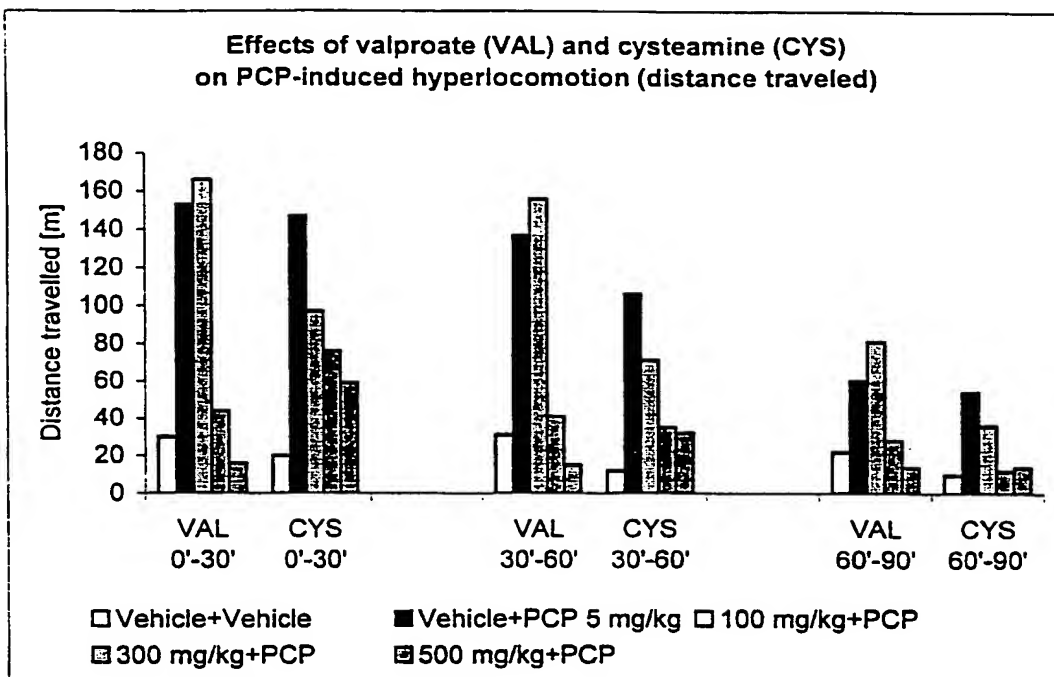
15 LITERATURE

- Bakker and Amini, Compr. Psychiatry 2, 1961, 269.
Benavides J., et al., Biochem. Pharmacol. 32, 1983, 287.
Carlsson et al., J Neural Transm - Gen Sect 95, 1994, 223.
Cheramy et al., Eur J Pharmacol 47, 1978, 141.
D'Souza D.C. et al., CNS Drugs Rev. 1, 1995, 227.
Freed et al., Neuropharmacology 23, 1984, 175.
Furuya et al., Brain Res 781, 1998, 227.
Giorguieff et al., J Physiol 75, 1979, 611.
Gleason et al., Psychopharmacology 129, 1997, 79.
Goff D.C. et al., Arch. Gen. Psychiatry 56, 1999, 21.
Goff, D.C. et al., Am. J. Psychiatry. 152, 1995, 1213.
Heresco-Levy U., Arch. Gen. Psychiatry 56, 1999, 29.
Hiraya et al., J. Biolog. Chem. 255, 1980, 11664.
Iwama H., et al., Biochem. Biophys. Res. Commun. 231, 1997, 793.
Jackson et al., Pharmacol Biochem Behav 48, 465.
Javitt et al., Biol Psychiatry 45, 1999, 668.
Javitt et al., Neuropsychopharmacology 1997, 17, 202.
Kikuchi Goro, et al. Biochem. Soc. Transactions, 1980, 504.

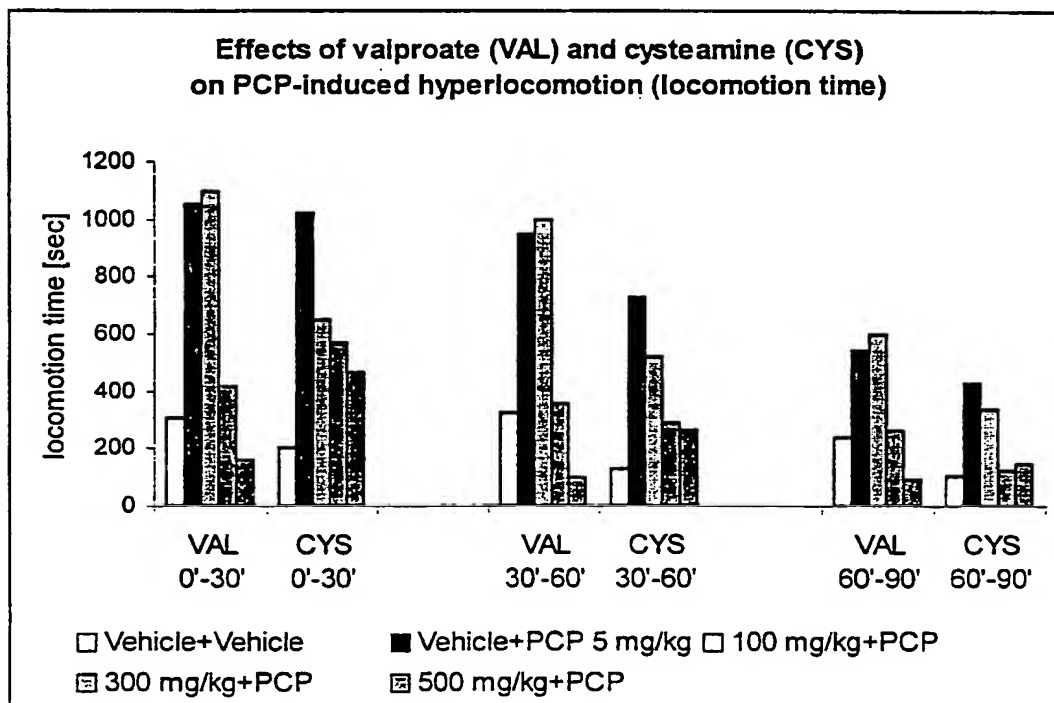
- Krebs-Thomson et al., Neuropsychopharmacology 18, 1998, 339
- Kretschmer and Koch, Psychopharmacology 130, 1997, 131.
- Kretschmer et al., J Neural Transm 87, 1992, 23.
- Krystal et al., Arch Gen Psychiatry 51, 1994, 199.
- Kume A., et al., J. Biol. Chem. 266, 1991, 3323.
- Kure S., et al., Jpn. J. Human Genet., 42, 1997, 13.
- Lathi et al., Neuropsychopharmacology 13, 1995, 9.
- Leviel et al., Brain Res 175, 1979, 259.
- Luby et al., Am J Psychiatry 119, 1962, 61.
- Luby et al., Arch Neurol Psychiatry 81, 1959, 363.
- Malhotra et al., Neuropsychopharmacology 14, 1996, 301.
- Malhotra et al., Neuropsychopharmacology 17, 1997, 141.
- Martin-Gallardo, et al., Biochem. Pharmacol. 34, 1985, 2877.
- Nankai et al., Prog Neuropsychopharmacol Biol Psychiatry 22, 1998, 35.
- Nilsson et al., J Neural Transm 104, 1997, 1195.
- Pratais et al., Psychopharmacology 50, 1976, 1.
- Puech et al., Eur J Pharmacol 50, 1978, 291.
- Rosenbaum et al., Arch Gen Psychiatry 1, 1959, 651.
- Schmidt and Kretschmer, Neurosci Biobehav Rev 21, 1997, 381.
- Singh et al., Proc Natl Acad Sci USA 87, 1990, 347.
- Toth and Lajtha, Neurochem Res 11, 1986, 393.
- Toth et al., Res Commun Psychol Psychiatry Behav 11, 1986, 1.
- Vanover, Eur J Pharmacol 332, 1997, 115.
- Zylberman I. et al., N.Y. Acad. Sci. 757, 1995, 487.

PATENT CLAIMS

1. Use of an inhibitor of the glycine cleavage system for the manufacture of a medicament for the treatment of a psychotic disorder in a human patient.
2. Use according to claim 1, wherein the psychotic disorder is selected from schizophrenia, major depression, manic-depressive disorder, Alzheimers disease or post-traumatic stress syndrome.
3. Use according to claim 2, wherein the inhibitor affects augmenting NMDA receptor-mediated neurotransmission.
4. Use according to claim 1 - 3, wherein the inhibitor of the glycine cleavage system is selected from valporate and cysteamine.



(A)



(B)

Fig. 1

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/03456

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/19 A61K31/13 A61P25/18 A61P25/24 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHNEIDER L.S. ET AL: "Mechanism of action and prospects for cognitive enhancing medications" MEDICAL CLINICS OF NORTH AMERICA, vol. 78, no. 4, 1994, pages 911-934, XP000917566 page 916; table 2	1-4
X	MARK R. J. ET AL: "Anticonvulsants attenuate amyloid beta-peptide neurotoxicity, Ca ²⁺ deregulation, and cytoskeletal pathology" NEUROBIOLOGY OF AGING, vol. 16, 1995, pages 187-198, XP000917338 abstract	1-4
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; Database accession no. prev199699205075 XP002146798 abstract & TAKAHASHI M. ET AL: "Case report of sodium valproate treatment of aggression associated with Alzheimer's disease" BRAIN AND NERVE (TOKYO), vol. 48, 1996, pages 757-760,	1-4
X	KECK P.E. ET AL: "Anticonvulsants and antipsychotics in the treatment of bipolar disorder" JOURNAL OF CLINICAL PSYCHIATRY, vol. 59, 1998, pages 74-81, XP000917401 "Valproate" page 74 -page 75	1-4
X	DAVIS L.L. ET AL: "Valproate as an antidepressant in major depressive disorder" PSYCHOPHARMACOLOGY BULLETIN, vol. 32, 1996, pages 647-652, XP000917554 abstract	1-4
X	HOLTZER C.D. ET AL: "Valproate in the treatment of acute mania" JOURNAL OF PHARMACY TECHNOLOGY, vol. 12, 1996, pages 6-11, XP000917438 page 11, last paragraph	1-4
X	HAYES S.G. ET AL: "Long-term use of valproate in primary psychiatric disorders" JOURNAL OF CLINICAL PSYCHIATRY, vol. 50, 1989, pages 35-39, XP000917324 abstract	1-4
X	MORINIGO A. ET AL: "Treatment of resistant schizophrenia with valproate and neuroleptic drugs" HILLSIDE JOURNAL OF CLINICAL PSYCHIATRY, vol. 11, 1989, pages 199-208, XP000917396 abstract	1-4
X	WO 94 05280 A (SALIM AWS SHAKIR MUSTAFA) 17 March 1994 (1994-03-17) claims	1-4
P,X	WO 99 49860 A (ENDOWMENT RES INHUMAN BIOLOGY ;VALLEE BERT L (US); MARET WOLFGANG) 7 October 1999 (1999-10-07) claims 22-34	1-4

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/03456

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
W0 9405280	A	17-03-1994	AU 4975193 A	29-03-1994
W0 9949860	A	07-10-1999	AU 3470399 A	18-10-1999

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